Introduction to Metabolism

Introduction

This lesson should be **first and last**. It'll make no sense on the initial run-through; it might even feel overwhelming. It may not be apparent how things fit together, but visually it'll be apparent that there is a connection. There are going to be arrows leading from this organ and that, ups and downs, different colors, differences in one cell vs. another. Yes, it's daunting, but when you complete the lessons and look again, you'll see how much you learned, and (we hope) even understand the layout.

This is the preview. **Don't expect to learn anything testable in this lesson. DO NOT try to follow the arrows or memorize the pathways**. Digest this as a foundation, so when we refer back to it, or ask you to think of this or that state, it's there in the back of your mind.

The goal is to explain the structure of the model—the **five cells of metabolism**, which cells have which resources, and which **energy source can be used by each cell** given the cell's properties and functions. We introduce the balance between glucagon and insulin as well.

The crux of the second lesson is the glucagon-insulin balance. We review what happens in each cell during the **glucagon-dominant state** and again during the **insulin-dependent state**. Because this is meant as an **overview and review**, the pathways are shortened and simplified. The goal is to see what happens **globally**—glucagon or insulin. There'll be plenty of depth to follow.

Sources of Energy

Carbohydrates are glucose. Even complex carbohydrates that include galactose or fructose are eventually combined in the glucose pathway. Glucose is the preferred fuel for all cells to do what they need to do, to get their ATP, their energy. Carbohydrates are either ingested (diet) or made by the liver.

Fatty acids are long chains of carbons. Even two carbons (one acetyl-CoA) contains energy. Fatty acids are the carbon chains sometimes referred to as "fat." "Fat" could also be the adipose cells, our chubby waistline, or the storage form of fatty acids called triglycerides in the adipose cells. Start thinking about fat as fatty acids. All cells (except RBCs) can use fatty acids in one way or another—either burning them for energy or using the liver's ketones that come from fatty acids.

Amino acids are from the catabolism of protein. Protein is never used directly as a source of energy (except in skeletal muscle). Instead, amino acids are sent to the liver to be turned into glucose, or burned for energy to make glucose. Most of metabolism is concerned with nitrogen metabolism rather than the amino acids.

The Hormone Balance

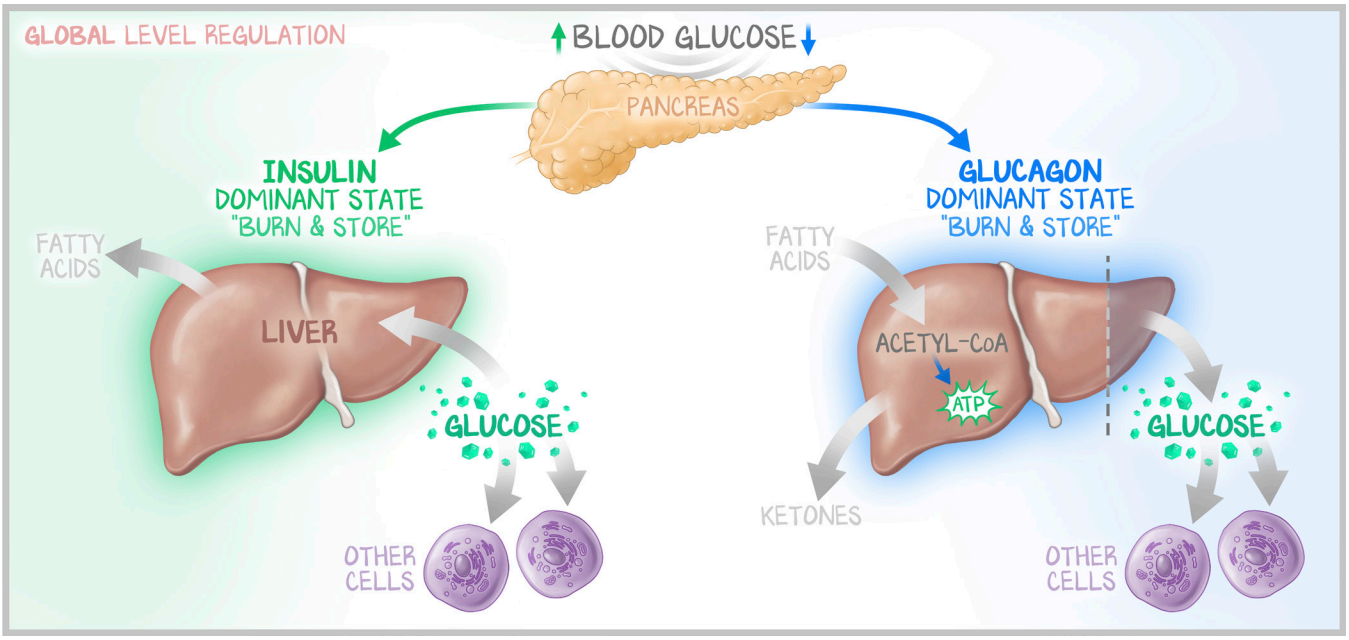

Figure 1.1: The Balance between Glucagon and Insulin
Insulin drives the body when eating, when dietary glucose can be used for energy. Glucagon drives the body when fasting, when hepatic glucose must be used for energy.

Homeostasis is controlled by the pancreas. The pancreas senses changes in blood sugar and directs the liver, which is the metabolism powerhouse, to move between two global states: insulin and glucagon.

During a meal, nutritional glucose is taken in. The pancreas senses the rise in the blood glucose, and in this "fed" state, **insulin turns on**. Insulin then becomes the dominant hormone between insulin and glucagon. In the **insulin-dominant state**, all cells are taking up blood glucose and **burning it for energy**, and some cells are also **storing it for later**.

In contrast, when the meal ends, and there's no longer an influx of glucose from the diet, the pancreas senses a drop in the blood glucose, turns insulin off, and **turns glucagon on**. Glucagon then becomes the dominant hormone between insulin and glucagon. In the **glucagon-dominant state**, most cells are still taking up blood glucose to **burn for energy**, but things get much more complicated. Effectively, there are reserve sources within cells that cells can draw on, but, for the most part the **glucagon-dominant state** is characterized by the **liver's production of glucose** and the need for **the liver to make ketones** for use by other tissues.

Whenever discussing a process or pathway, it's imperative to know which cell it's in and what the **dominant hormone is**. The nuances matter. Again, this is the overview; the details you need are up next.

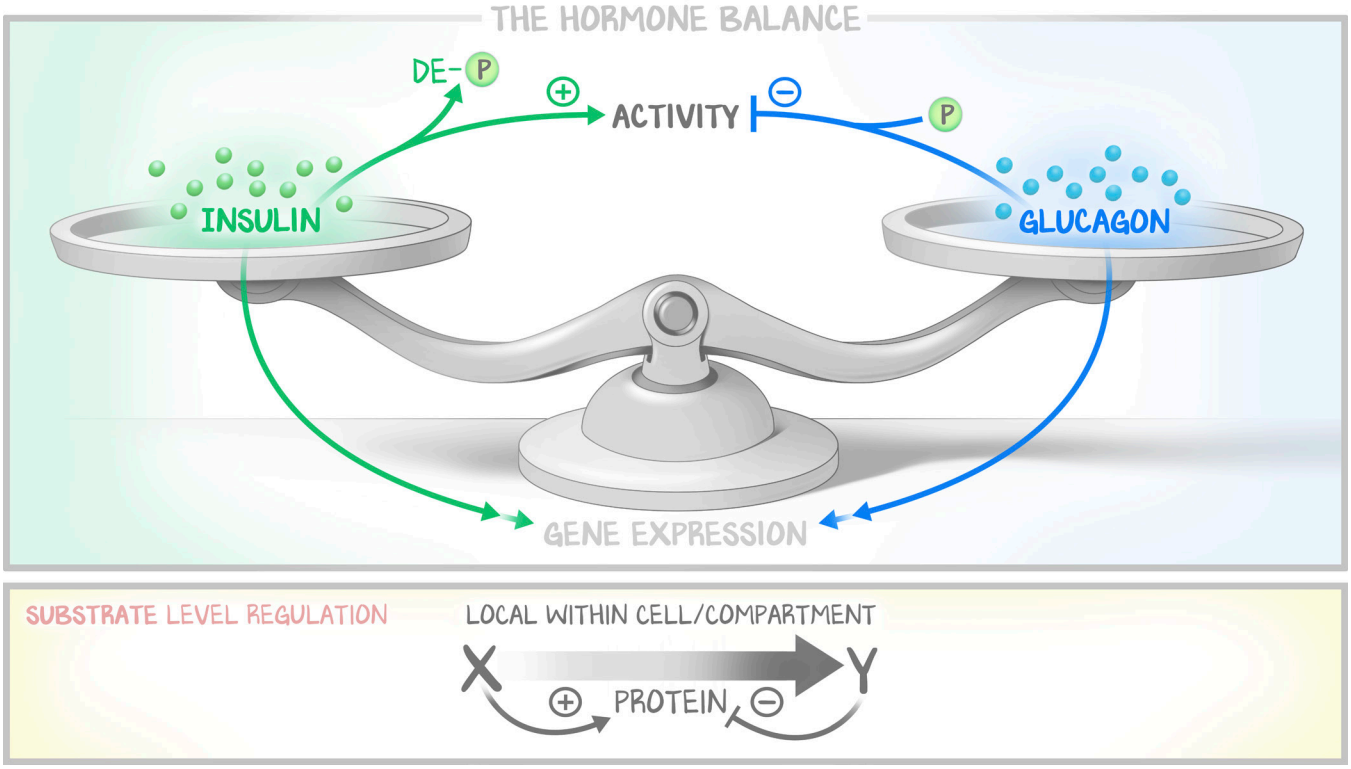

Figure 1.2: The Balance between Glucagon and Insulin

Five Different Cells Demonstrate the Breadth of Cellular Capabilities

These five cells illustrate the differences between all tissues. Some cells are more sophisticated than others, capable of generating energy in multiple ways. Some are more selfish (using what is made but making nothing) and some are more giving (either supplying the liver with something to make nutrients for all cells or being the liver itself, whose whole purpose is to supply all other cells between meals).

All cells default to "make ATP." They do this regardless of the dominant hormone. "Make ATP," though, is highly variable. We escalate in terms of complexity:

Red blood cells have **no mitochondria**. Red blood cells are effectively the model for **anaerobic metabolism**. Because they have no mitochondria, they can't do anything except take glucose from the periphery. They can't make glycogen.

Brain cells are **highly metabolically active**. They're active all the time. No downtime means zero opportunity to store energy. Therefore, these active cells must continuously receive energy. The preferred energy source is glucose. But they **do have mitochondria**, so are able to amplify ATP production with **oxidative phosphorylation**. Despite their mitochondria, brain cells are needy. They don't have glycogen and they can't oxidize fatty acids. They use **glucose**—glycolysis-PDH-TCA-ETC—or, in severe conditions, can use ketone bodies (but don't like it). They **need the liver to make it for them**.

Skeletal muscle is also active but has periods of downtime. Skeletal muscle cells have mitochondria. Skeletal muscle relies on the liver to make glucose as well. But the skeletal muscle will contract irrespective of the hormone state of the body, and so needs some localized form of readily accessible energy. The skeletal muscle can **build and utilize glycogen stores, and can use fatty acids** through oxidation. Skeletal muscle **likes ketone bodies**. They're actually the preferred energy source, after the glycogen runs out. Skeletal muscle cells, like RBCs and brain cells, are selfish. They take energy from

glucose and ketones, but don't really offer anything back. They CAN enter **nitrogen metabolism / protein catabolism**, but that happens only when there's prolonged fasting. Look at skeletal muscle as a slightly more sophisticated neuron—one that can store its own glycogen, use ketones, and do a little fatty acid oxidation. But, like the brain, the muscle will use substrates to send them down the TCA-ETC, using ATP to fuel its main function (contract).

Adipose is a special case. Sure, the adipose cell needs ATP, just like all cells, which it gets from glycolysis-PDH-TCA-ETC. But its main purpose is to **store lipids for the liver**, then **mobilize lipids to the liver**. But although the cells have been presented in an ascending fashion, "adding function" as we've gone down the list, adipose isn't just skeletal muscle with an extra function. Adipose has mitochondria, can **oxidize its own fatty acids**, stores and mobilizes fatty acids for the liver . . . and does little else. It's a reservoir for substrate for the liver. The way adipose gets its energy is via mitochondria, using the TCA and ETC to get ATP. When it has enough ATP, it can then do its other functions (store or mobilize fat).

The **liver** is the **epicenter of metabolism**, and will command most of our attention. It can do everything. There's nothing another cell can do that the liver can't (except use ketones). But especially important is the fact that the liver has been programmed away from the default—everything the liver does is to **make glucose for all other cells**, and **ketone bodies** for some cells. It will take care of itself first, ensuring that the hepatocytes are flush with ATP before trying to help others, but the liver is the site of **fatty acid oxidation** (mitochondria), **fatty acid synthesis** (cytoplasm), glycolysis (cytoplasm), and **gluconeogenesis** (cytoplasm). It can store and access **glycogen** (cytoplasm), and **metabolize nitrogen**. While the liver does fill up its own energy stores with TCA-ETC, once flush it'll then do all sorts of things to get energy to other cells.

The only thing the liver doesn't do is use **ketone bodies**—it's too busy making them.

Making the Switch from Hormone to Hormone

Pay attention to regulation of key enzymes at each step throughout the course. Effectively what happens is that **substrate-level control** within the cytoplasm helps **prioritize** the pathways, while **hormone-level control** determines what state the body is in. The pancreas senses the **whole-body state** and adjusts **insulin** and **glucagon** to match whatever state the patient is in, whole body.

What's cool about how it works is that the **substrate-level control** is regulated second to second. As hormones change, some hormones work on some proteins by phosphorylating. This allows changes in the minute-to-minute range. And at the same time, those same hormones **induce gene expression of proteins**, taking longer to act but also making a longer-lasting impact with synthesis of new proteins.

You're not expected to have a eureka moment, or even supposed to recognize all the words. Come back to this after Metabolism is completed and see just how much you know.

	LESSON	TITLE	RBCS	BRAIN	SK MUSCLE	ADIPOSE	LIVER
Carbohydrate Metabolism	3	Glycolysis	+	+	+	+	+
	4	Pyruvate Dehydrogenase	-	+	+	+	+
	5	Citric Acid Cycle	-	+	+	+	+
	6	Electron Transport Chain	-	+	+	+	+
	7	Electron Transport Chain Pharm	-	+	+	+	+
	8	Gluconeogenesis	-	-	-	-	+
	9	Carbohydrate Regulation					
	10	Galactose and Fructose					
	11	Glycogen	-	-	+	+	+
	12	Glycogen Disorders	-	-	+	+	+
Fatty Acid Metabolism	13	Fatty Acid Synthesis	-	-	-	-	+
	14	Triglycerides and Cholesterol	-	-	-	-	+
	15	Fatty Acid Oxidation	-	-	+	+	+
	16	Ketones	-	+	+	+	+
	17	Sphingolipids					
Protein Metabolism	18	Nitrogen Metabolism	-	-	+	-	+
	19	Urea Cycle	-	-	+	-	+
	20	Disorders of Amino Acids	-	-	+	-	+

Table 1.1